REMARKS

Claims 8-10, 58, 59, 62-65, 77, 79, 88, 89 and 97 have been cancelled. Claims 1, 11-13, 22, 26, 31, 40, 41, 46, 60, 61, 66, 70-72, 80-82, 84-87, 90-96 and 98 have been amended.

Claims 1, 13, 22, 26, 31, 40, 41, 46, 66, 70-72, 80-82, 84-87, 90-96 and 98 have been amended to recite "humanized immunoglobulin" and "antigen-binding fragment." Support for these amendments is found, for example, at page 13, lines 5-10.

Claims 1, 22, 40 and 80 have been amended to recite "[a] method for treating a human having an inflammatory bowel disease..." Support for this amendment is found, for example, at page 15, lines 16-21.

Claims 1, 22 and 40 have been further amended to recite specific sequences for heavy chain CDRs 1, 2 and 3 and light chain CDRs 1, 2 and 3. Support for this amendment is found, for example, at page 11, lines 4-6 and in Figure 5.

Claims 11, 12, 60 and 61 have been amended to correct dependencies.

Withdrawal of §112, First Paragraph Rejections

Applicants thank the Examiner for withdrawing the rejection of claims 1, 13, 18, 22, 26, 31, 36, 40, 41, 46, 51, 55-60, 62 and 70-79 under 35 U.S.C. § 112, first paragraph.

Rejection of Claims 1, 8-13, 18, 22, 26, 31, 36, 40, 41, 46, 51, 55-60, 62-64, 73-83 and 93-97 Under 35 U.S.C. § 103(a)

Claims 1, 8-13, 18, 22, 26, 31, 36, 40, 41, 46, 51, 55-60, 62-64, 73-83 and 93-97 are rejected under 35 U.S.C. §103(a) as being unpatentable over Ponath *et al.* (WO 98/06248) in view of Gordon *et al.* (Reference AS5 of record) or Gordon *et al.* (Reference AT5 of record).

The Examiner maintains that Ponath *et al.* disclose treatment of ulcerative colitis with humanized LDP-02 antibody, wherein said antibody has the amino acid sequence recited in the claims. The Examiner further states that Ponath *et al.* disclose that the dosage and schedule of administration used would be determined using routine experimentation, that the antibody can be administered in multiple doses, and that the patient can additionally receive steroids or

sulfasalazine or other immunosuppressive agents. The Examiner admits that Ponath *et al.* do not disclose the particular claimed administration protocols. (Office Action, page 3).

The Examiner further maintains that the Gordon *et al.* references disclose that patients with inflammatory bowel disease or ulcerative colitis can be treated with a dose of 3 mg of humanized antibody against an α4 integrin, wherein said dosage is a starting point for future clinical studies. In the Examiner's opinion, a routineer would have started with the 3 mg/kg dosage disclosed by Gordon *et al.* and arrived at the claimed protocols using routine experimentation.

Applicants respectfully disagree. Although it may be routine for a scientist to have a desire to improve upon what is already generally known, one of ordinary skill in the art would not consider the dosage of an unrelated antibody as a starting point for which to begin testing a different antibody. The courts have found that potential solutions are less likely to be genuinely predictable in the chemical arts. *See* Eisai Co. v. Dr. Reddy's Laboratories, Inc. (Fed. Cir. 2008). In *KSR*, the Supreme Court noted that an invention may have been obvious when there was a design need or market pressure to solve a problem and there were a finite number of identified, predictable solutions. The Supreme Court's analysis relies on several assumptions about the prior art landscape: (1) a starting reference point or point in the art, prior to the time of invention, from which a skilled person might identify a problem and pursue potential solutions; (2) that the record up to the time of the invention would give some reasons to make particular modifications to achieve the claimed result; and (3) that the record before the time of the invention would supply some reasons for narrowing the prior art universe to a finite number of identified, predictable solutions. To the extent an art is unpredictable, as the pharmaceutical arts often are, *KSR*'s focus on these "identified, predictable solutions" may present a difficult hurdle because potential solutions are less likely to be genuinely predictable.

The combined teachings of Ponath *et al.* and the Gordon *et al.* references, at best, would provide a method for treating ulcerative colitis by administering an antibody at a single dose of 3 mg/kg. If, for arguments sake, the person of skill in the art was motivated to use the dose of 3 mg/kg as a starting point for optimizing treatment within the disclosed range, the results would still be unpredictable and require undue experimentation.

As evidenced by Reference AV5 and AW5, cited in the Supplemental Information Disclosure Statement filed concurrently herewith, clinical trials are not routine or predictable. Figure 1 of Kola *et al.* shows that of the new drugs that are tested in man, only about 1 in 10 (11%) successfully complete clinical trials and achieve and FDA registration. Rather, to the contrary, most drug trials are failures. Thus, as previously held by the courts, the chemical and pharmaceutical arts are unpredictable and a mere starting point does not lead one of skill in the art to an identified, predictable solution.

Unexpected Results

The Examiner also states that the study disclosed in the specification that shows that antibody LDP-02 has superior efficacy, as measured by reduction in the PT score, even when six-times less antibody is used than was used in Gordon *et al*, is not germane to the claimed methods because a single dose was administered in the study. (See Table 23 at page 45 and Amendment filed April 14, 2008 at page 14-15, regarding the superior efficacy disclosed in the application.)

The Examiner has provided no reasoning to establish that the superior effect seen after a single dose of LDP-02 would not also be seen if more than one dose were administered.

Indeed, further experimental data in support of the claimed invention has been generated by the applicant. In this regard, the applicant has sponsored a phase 2 study to assess the efficacy and safety of MLN0002 (a humanized antibody to $\alpha 4\beta 7$ integrin that contains the six CDRs specified in claim 1). In this study, the humanized antibody was administered at a dose of 2.0mg/kg or 0.5mg/kg by intravenous infusion on days 1 and 29 to patients with active Crohn's disease (an IBD). (i.e. an initial dose followed by one or more subsequent doses was administered to patients having IBD). Clinical response rates at day 57 were 53% and 49% respectively compared to 41% for patients receiving a placebo dose. Clinical remission rates at day 57 were 37% and 30% respectively compared to 21% for patients receiving a placebo dose. The study concluded that there could be a dose-dependent beneficial effect of the humanized antibody on clinical remission. This provides further evidence in support of unexpected results for the claimed subject matter. A copy of a publication from Clin Gastroenterol Hepatol. 6(12)

1370-1377, (2008) summarizing the study is included in the Supplemental Information Disclosure Statement filed concurrently.

Furthermore, additional data has been generated showing that MLN0002 administration has an effect on patients suffering from ulcerative colitis (an example of IBD). In this study, 181 patients were randomly assigned to receive 0.5mg/kg or 2.0mg/kg of the humanized antibody. The humanized antibody was administered at a dose of 2.0mg/kg or 0.5mg/kg by intravenous infusion on days 1 and 29 to patients with active ulcerative colitis (an IBD). (i.e. an initial dose followed by one or more subsequent doses was administered to patients having IBD). Clinical remission rates at week six were 33% and 32% for patients receiving 0.5mg/kg or 2.0mg/kg respectively compared to 14% for patients receiving a placebo dose. In this study it was concluded that the humanized immunoglobulin specific for $\alpha 4\beta 7$ integrin was effective for induction of clinical and endoscopic remission in patients with active ulcerative colitis. This provides further evidence in support of unexpected results for the claimed subject matter. A copy of a publication from N Engl J Med, 352, 2499-2507, (2005) summarizing this study is included in the Supplemental Information Statement filed concurrently.

The claimed invention is not obvious over the cited references because none of the references either individually or in combination suggest the claimed methods of treatment and the results of the method of treatment are unexpected.

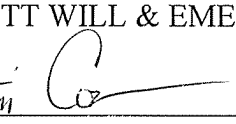
CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the

Examiner is invited to call the undersigned.

Respectfully submitted,

MCDERMOTT WILL & EMERY LLP

By 

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